Cyclotron Production of ^{99m}Tc: An Approach to the Medical Isotope Crisis

From the Newsline editor: Strategies to counter increasingly challenging and unpredictable medical isotope supply shortages have ranged from proposals to build new networks of nuclear reactors to requirements for higher levels of coordination and cooperative planning among existing international producers. Here, a group of Canadian academic and industry researchers propose a different solution with potential for near-term implementation.

Direct production of ^{99m}Tc from isotopically enriched ^{100}Mo via proton bombardment has received little attention, despite the fact that measured production yields indicate that up to 1.4 TBq of ^{99m}Tc can be produced in 6 h using a high-current, medium-energy medical cyclotron. If produced with suitable radioisotopic and chemical purity, such an amount of ^{99m}Tc would suffice to fulfill the requirements of a large metropolitan area. We compared the chemical, radiochemical, and biologic properties of cyclotron- and generator-derived ^{99m}Tc for common nuclear imaging procedures. Our results, presented here for Newsline readers, suggest that a medical cyclotron can produce U.S. Pharmacopeia (USP)–compliant, Good Manufacturing Practice (GMP)–grade ^{99m}Tc radiopharmaceuticals that can be used as a substitute for generator-derived ^{99m}Tc radiopharmaceuticals for nuclear imaging procedures. Direct production of ^{99m}Tc using cyclotrons can be considered as a potential means to alleviate the current (and recurrent) challenges in isotope supply. Implementing networks of medium-energy, high-current medical cyclotrons would reduce reliance on nuclear reactors and attenuate the negative consequences associated with the use of fission technology.

Background

Since 1947, when Carlo Perrier and Emilio Segrè (*1*) proposed the name *technetium* for element 43, metastable ^{99m}Tc ($T_{½}$ = 6 h) has evolved as the most widely used radioisotope in nuclear medicine. A variety of ^{99m}Tc-labeled radiopharmaceuticals are now used daily in about 70,000 medical imaging procedures worldwide (*2*). The principal producers of ^{99m}Tc, the National Research Universal reactor (Chalk River, Canada) and the High Flux Reactor (Petten, The Netherlands), until recently produced about two-thirds of the world's requirements for ^{99m}Tc (*3*). Neutron flux in these reactors induces fission of highly enriched ^{235}U, producing a variety of radioactive products, including ^{99}Mo ($T_{½}$ = 67 h). After purification the ^{99}Mo is absorbed on aluminum oxide providing a ^{99}Mo/^{99m}Tc generator from which the ^{99m}Tc is eluted as a sterile pertechnetate ($^{99m}TcO_4^-$) solution. Although ^{99m}Tc-pertechnetate is used for thyroid imaging, most applications involve incorporating the ^{99m}Tc in selected carriers with commercially available kits to yield specific ^{99m}Tc radiopharmaceuticals suitable for planar (2D) scintigraphic imaging and 3D SPECT of major medical conditions, such as heart and lung function and cancer.

With the abundant availability of ^{99m}Tc from reactor-produced ^{99}Mo/^{99m}Tc generators, potential alternative sources of ^{99m}Tc received little attention until recently (*4*). Current global interruptions of ^{99}Mo supply, aging reactors, and the staggering costs of their maintenance have accelerated the search for alternative sources of ^{99m}Tc (*5*). One such alternative source that does not involve uranium fission is the direct formation of ^{99m}Tc by proton bombardment of isotopically enriched ^{100}Mo. Highly enriched ^{100}Mo (>99.5%) is readily available from multiple suppliers at an affordable price in either metal or oxide forms. The feasibility of ^{99m}Tc production with a compact cyclotron in terabecquerel quantities via the ^{100}Mo (p,2n) ^{99m}Tc nuclear reaction was demonstrated as early as 1971 by Beaver and Hupf (*6*) and confirmed by a number of researchers (*7*), with the most recent publications by Scholten et al. (*8*) and Takács et al. (*9*). We compared the chemical and radiochemical properties and in vivo behavior of cyclotron-produced ^{99m}Tc with that of ^{99}Mo/^{99m}Tc generator-produced ^{99m}Tc.

Comparing Cyclotron-Produced ^{99m}Tc with ^{99}Mo/^{99m}Tc Generator-Produced ^{99m}Tc

Preparation. Generator-produced ^{99m}Tc was obtained from a ^{99}Mo/^{99m}Tc generator (Lantheus IM; Montreal, Canada). Cyclotron-produced ^{99m}Tc was prepared by the ^{100}Mo (p,2n) ^{99m}Tc nuclear reaction using a TR-19 cyclotron (ACSI; Richmond, Canada). Small targets (6-mm diameter discs) were prepared by melting sintered ^{100}Mo pellets (110–153 mg, 99.54% enrichment) onto tantalum backing supports. Targets were bombarded for 1.5–3 h with 15.5–17.0 MeV protons (14–52 μA) using the TR-19 cyclotron. After bombardment, ^{100}Mo targets were partially dissolved by electrochemical dissolution in 1N HCl in the presence of H_2O_2 (25%) and purified by the method of Chattopadhyay et al. (*10*). After addition of 2 mL of 5 N NaOH, Tc and Mo were trapped on Dowex-1 × 8 resin (25 mg, 200–400 mesh). Molybdenum was eluted from the column with 3 mL of saline. Technetium was eluted from the column as [^{99m}Tc]TcO_4^- (pertechnetate) using 5 mL of a 0.2 mg/mL tetrabutylammonium bromide solution in dichloromethane. The pertechnetate was absorbed on a neutral alumina column

(1.5 g) and eluted with physiologic saline (3–5 mL) to yield the purified ^{99m}Tc-pertechnetate solution.

Radionuclide purity of the cyclotron-produced ^{99m}Tc was assessed by γ spectroscopy for the presence of ^{99}Mo, from the ^{100}Mo (*p*,*pn*) ^{99}Mo reaction, and of ^{97}Nb, from the ^{100}Mo (*p*,α) ^{97}Nb reaction. After allowing ^{99m}Tc to decay for 4 d, the presence of ^{96}Tc ($T_{½}$ = 4.28 d), ^{95}Tc ($T_{½}$ = 20 h) and ^{95m}Tc ($T_{½}$ = 61 d) was also measured by γ spectroscopy. The radiochemical purity of cyclotron-produced [^{99m}Tc]TcO_4^- was determined by instant thin-layer chromatography (ITLC) on Whatman 3MM chromatographic paper developed with acetone/HCl 2N (80:20).

For imaging studies, both cyclotron- and generator-produced ^{99m}Tc were formulated as 3 different radiopharmaceuticals: ^{99m}Tc-pertechnetate for thyroid imaging, ^{99m}Tc complex with methylene diphosphate (^{99m}Tc-MDP) for bone scanning, and ^{99m}Tc complex with hexakis-2-methoxy*iso*butyl *iso*nitrile (^{99m}Tc-MIBI) for heart imaging. These radiopharmaceuticals account for more than 75% of all routine ^{99m}Tc scans currently used in diagnostic nuclear medicine (*11*). The latter 2 radiopharmaceuticals were prepared using commercially available MDP (Draximage Inc.; Montreal, Canada) and MIBI (Cardiolite, Lantheus IM Inc.; Montreal, Canada) kits. Labeling efficiencies for ^{99m}Tc-MDP and ^{99m}Tc-MIBI were determined by ITLC following USP procedures.

Animal Scans. The biodistributions of ^{99m}Tc-pertechnetate, ^{99m}Tc-MDP, and ^{99m}Tc-MIBI, prepared with either cyclotron- or generator-produced ^{99m}Tc, were assessed in a healthy rat model. All animal experiments were conducted in male rats (220–260 g; Charles River Breeding Laboratories; Montreal, Canada), in accordance with the recommendations of the Canadian Council on Animal Care and the in-house ethics committee for Animal Experiments of the Université de Sherbrooke. For each experiment, 2 animals, under isofluorane anesthesia, were placed side by side ventrally on the high-resolution collimator of a GE XRT γ camera (GE Healthcare; Waukesha, WI). Both rats were simultaneously injected via a catheter installed in the tail vein with a 0.3-mL physiologic saline solution containing 34–90 MBq of the selected ^{99m}Tc-radiopharmaceutical, prepared either with cyclotron- or generator-produced ^{99m}Tc. Dynamic acquisitions were continued over a 2-h period with the following scanning sequence: 60·1 s (64 × 64), 20·1 min (128 × 128), 20·3 min (128 × 128), 6·5 min (128 × 128), and 1·10 min (128 × 128). At the end of scanning, the rats were killed and dissected to measure activities of target tissues.

Results. Up to 12 GBq of ^{99m}Tc were produced in each bombardment. After bombardment, ^{100}Mo targets were partially dissolved and purified to give 0.7–1.1 GBq of ^{99m}Tc-pertechnetate for in vivo assays. Chemical processing was completed in <1 h. The radionuclide purity of the cyclotron-produced ^{99m}Tc was >99.99%, as assessed by γ spectroscopy, exceeding USP requirements for generator-based ^{99m}Tc. Although small peaks corresponding to ^{99}Mo were observed in the initial solute, these were not detectable in aliquots of the purified ^{99m}Tc-pertechnetate solution, indicating that the ^{100}Mo target material was quantitatively separated from the technetium. Minute amounts of ^{97}Nb observed in the target solute were also quantitatively separated from ^{99m}Tc-pertechnetate during processing.

The content of other technetium isotopes was measured after allowing sufficient time (4 d) for ^{99m}Tc decay, with the presence of 0.0010% ^{95}Tc, 0.0014% ^{96}Tc, and <0.0003% ^{95m}Tc at the end of bombardment determined by γ spectroscopy, below USP requirements of 0.01% for generator-produced ^{99m}Tc. No other radionuclidic impurities were found. The radiochemical purity of cyclotron-produced [^{99m}Tc]TcO_4^- was >99.5%, also meeting the USP requirement of 95%. The content of groundstate ^{99}Tc ($T_{½}$ = 2.1 × 10^5 y) was not determined in this experiment but will be one of the tasks for future work. The labeling efficiency, which potentially could be affected by the presence of large quantities of ground state technetium, was also well above USP requirements (>90%): 98.4% for ^{99m}Tc-MDP and 98.0% for ^{99m}Tc-MIBI.

Static images of healthy rats obtained 2 h after intravenous administration of each of these ^{99m}Tc-radiopharmaceuticals show matching ^{99m}Tc distribution patterns, within normal interindividual variations between each pair of animals, clearly delineating the thyroid with ^{99m}Tc-pertechnetate, skeleton with ^{99m}Tc-MDP, and heart with ^{99m}Tc-MIBI (Fig. 1). Uptake kinetics calculated over the 3 target organs delineated in Figure 1 (thyroid, bones, and heart) show identical patterns for the cyclotron- and generator-produced ^{99m}Tc-radiopharmaceuticals (Fig. 2). Tissue activities from dissected samples collected 30 min

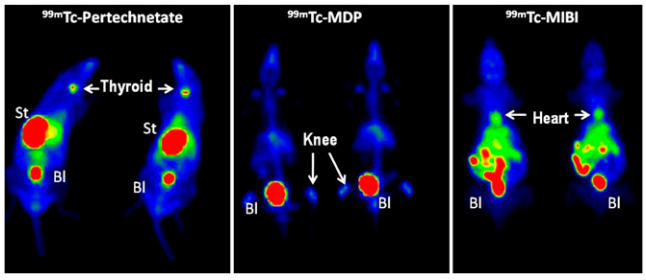

Figure 1. Anterior whole-body planar scintigrams of healthy rats 2 h after intravenous administration of: (left panel) 90 MBq of ^{99m}Tc-pertechnetate; (middle panel) 34 MBq of ^{99m}Tc-MDP; (right panel) 15 MBq of ^{99m}Tc-MIBI, prepared from cyclotron-produced ^{99m}Tc (right image) or commercially available ^{99}Mo/^{99m}Tc generator-produced ^{99m}Tc (left image). In the case of ^{99m}Tc-pertechnetate, radioactivity is mainly concentrated in the stomach (St), bladder (Bl), and thyroid, which follows the expected distribution pattern for this radiotracer. With the bone-imaging tracer ^{99m}Tc-MDP, most radioactivity is concentrated in the spine, knees, shoulders, and skull; some radioactivity is also seen in the liver, and most radioactivity is excreted through the bladder (Bl). With the cardiac-imaging tracer ^{99m}Tc-MIBI, the heart is clearly delineated and most of the radioactivity is excreted via the intestines and bladder (Bl).

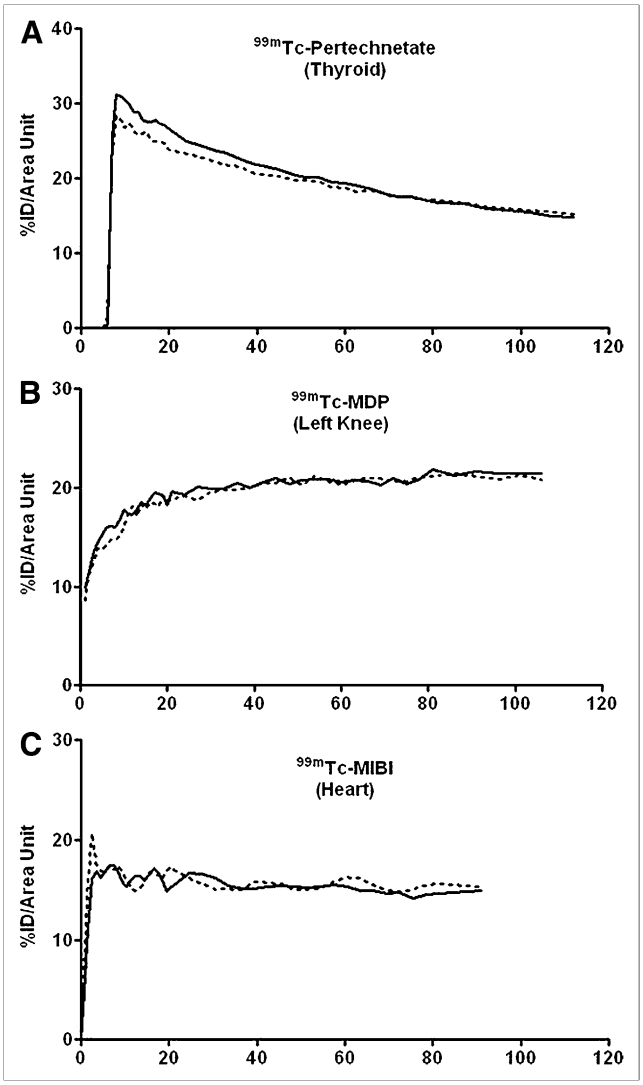

Figure 2. Time/radioactivity curves derived from regions of interest drawn around target organs on whole-body planar scintigrams of healthy rats (Fig. 1) after intravenous administration of ^{99m}Tc-pertechnetate (A), ^{99m}Tc-MDP (B), or ^{99m}Tc-MIBI (C) prepared from cyclotron-produced ^{99m}Tc (dotted line) or commercially available ^{99}Mo/^{99m}Tc generator-produced ^{99m}Tc (solid line). Radioactivity is expressed as percentage of injected dose per unit area (%ID/unit area) corrected for radioactive decay.

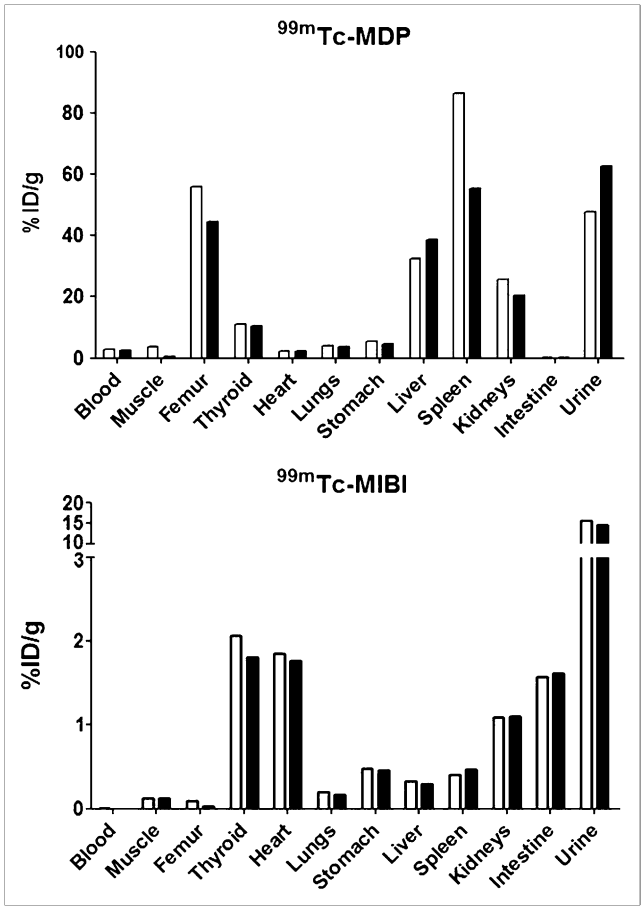

Figure 3. Tissue uptake in healthy rats, expressed as percentage of injected dose per gram of tissue (%ID/g), 2.5 h after intravenous injection of 34 MBq of ^{99m}Tc-MDP or 15 MBq of ^{99m}Tc-MIBI, prepared from cyclotron-produced ^{99m}Tc (open bars) or ^{99}Mo/^{99m}Tc generator-produced ^{99m}Tc (solid bars).

after the end of imaging with ^{99m}Tc-MDP and ^{99m}Tc-MIBI also show matching patterns between cyclotron- and generator-derived ^{99m}Tc preparations (Fig. 3). The higher spleen uptake with the cyclotron-produced ^{99m}Tc-MDP likely reflects the presence of a small quantity of $^{99m}TcO_2$ resulting from oxidation during chemical processing (*12*).

^{99m}Tc production rates of 0.6 GBq/μA/h at 24 MeV measured by Scholten et al. (*8*) and later confirmed by Tacaks et al. (*9*) indicate that up to 2.75 TBq of ^{99m}Tc can be produced in two 6-h bombardments at 500 μA using a medium-energy cyclotron. Assuming 15% ^{99m}Tc losses during processing, an average patient injection of 0.9 GBq, and 10 h decay for processing, delivery, and holding in the hospital, this amount would be sufficient to prepare 800 doses of ^{99m}Tc radiopharmaceuticals—the daily requirements for a population of ~5–7 million individuals (*13*). Regional distribution of cyclotron-produced ^{99m}Tc can be modeled after the well-established distribution networks of short-lived radiopharmaceuticals used for high-resolution 3-D PET imaging. Preparation and distribution of individual patient doses to hospitals and radiopharmacies would remain identical to current practices. Production of short-lived PET radiopharmaceuticals is mainly required during working hours, whereas ^{99m}Tc can be produced overnight, thus optimizing the use of medical cyclotrons.

Conclusion

The results of our quality control tests and in vivo experiments support the concept that cyclotron-produced ^{99m}Tc is suitable for preparation of USP-compliant, GMP-grade ^{99m}Tc radiopharmaceuticals. Establishing decentralized networks of medium-energy cyclotrons capable of producing large quantities of ^{99m}Tc would effectively complement the supply of medical isotopes traditionally provided by nuclear reactors, while sustaining the expanding need for other medical isotopes, including short-lived

positron emitters for PET imaging. Global interruptions of ^{99}Mo supply, aging reactors and the high costs of their maintenance, radioactive waste processing, and final reactor decommissioning make the use of safe and relatively low-cost cyclotron technology more attractive today for regional supply of ^{99m}Tc and other medical isotopes while facilitating the expanding role of high-resolution 3-D PET imaging in diagnostic nuclear medicine.

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